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Effects of different ACE inhibitor combinations on albuminuria: results of the GUARD study

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Clinical practice guidelines recommend blockers of the renin-angiotensin system alone or in combination with other agents to reduce blood pressure and albuminuria in patients with type 2 diabetes. Dihydropyridine calcium channel blockers, however, may lower blood pressure but not albuminuria in these patients. Here we tested the hypothesis that combining an ACE inhibitor with either a thiazide diuretic or a calcium channel blocker will cause similar reductions in blood pressure and albuminuria in hypertensive type 2 diabetics. We conducted a double blind randomized controlled trial on 332 hypertensive, albuminuric type 2 diabetic patients treated with benazepril with either amlodipine or hydrochlorothiazide for 1 year. The trial employed a non-inferiority design. Both combinations significantly reduced the urinary albumin to creatinine ratio and sitting blood pressure of the entire cohort. The percentage of patients progressing to overt proteinuria was similar for both groups. When we examined patients who had only microalbuminuria and hypertension we found that a larger percentage of the diuretic and ACE inhibitor normalized their albuminuria. We conclude that initial treatment using benzaepril with a diuretic resulted in a greater reduction in albuminuria compared to the group of ACE inhibitor and calcium channel blocker. In contrast, blood pressure reduction, particularly the diastolic component, favored the combination with amilodipine. The dissociation between reductions in blood pressure and albuminuria may be related to factors other than blood pressure.

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A coexistent diagnosis of hypertension and diabetes mellitus increases the risk for adverse cardiovascular and renal outcomes. This increased risk for adverse outcomes extends to a diastolic blood pressure (DBP) as low as 83 mm Hg and a systolic BP (SBP) as low as 127 mm Hg.[1,2] Microalbuminuria, an early clinical marker of vascular dysfunction in the kidney, is a strong prognostic indicator of both mortality and cardiovascular disease in patients with hypertension and diabetes.[3,4] In the Heart Outcomes Prevention Evaluation (HOPE), patients with microalbuminuria at baseline had an increased risk of the combined end point of myocardial infarction, stroke, or cardiovascular death irrespective of their diabetes status.[5]

Important therapeutic strategies to slow the decline in kidney function includes both aggressive BP reduction to a goal of $<130/80$ mm Hg in patients with hypertension and diabetes,[1,4,6] as well as a greater than 30% reduction in albuminuria.[7] More than 75% of these patients will require a combination of a renin–angiotensin system blocker with either a diuretic or calcium antagonist to achieve these guideline goals.[1,2,8] The Gauging Albuminuria Reduction With Lotrel in Diabetic Patients With Hypertension (GUARD) trial tested initial combination therapy of either a dihydropyridine calcium channel blockers or thiazide diuretic combined with the same angiotensin-converting enzyme (ACE) inhibitor in the reduction of blood pressure (BP) and albuminuria in patients with hypertension and type II diabetes. Changes in the urinary albumin excretion as assessed by a spot albumin-to-creatinine (Ualb:Cr) ratio after 52 weeks of treatment were compared in patients with hypertension, type II diabetes, and albuminuria randomized to a fixed-dose ACE inhibitor/calcium channel blockers (CCB) combination (benazepril/amlodipine; B + A) or fixed-dose ACE inhibitor/diuretic combination (benazepril/hydrochlorothiazide; B + HCTZ). The rationale and design of the study are described elsewhere.[9]

RESULTS

Patients

Of the 332 patients (166 in each group) randomized to treatment, 65 (27 patients, B + A; 38, B + HCTZ) patients

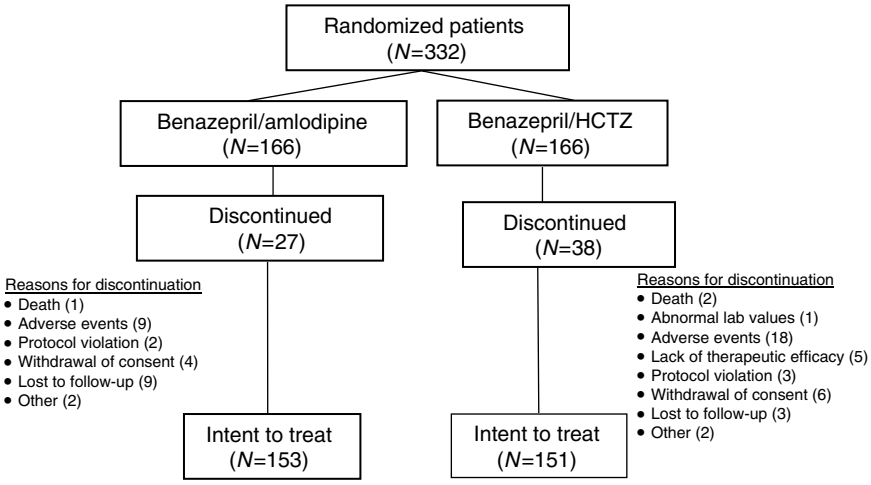

Figure 1 | Patient disposition.

Table 1 | Baseline demographic and clinical characteristics of all patients randomized to treatment (safety population)

Characteristic	Benazepril/amlodipine (*n*=166)	Benazepril/HCTZ (*n*=166)
Age (years), mean (± s.d.)	57.7 (± 10.9)	57.7 (± 10.9)
Age group, n (%)		
<65 years	121 (72.9)	118 (71.1)
⩾65 years	45 (27.1)	48 (28.9)
Gender, n (%)		
Male	109 (65.7)	108 (65.1)
Female	57 (34.3)	58 (34.9)
Race, n (%)		
White	107 (64.5)	93 (56.0)
Black	36 (21.7)	51 (30.7)
Asian	4 (2.4)	1 (0.6)
Other	19 (11.4)	21 (12.7)
Mean sitting BP, mm Hg ± s.d.		
Systolic	150 ± 13.3	151 ± 13.1
Diastolic	88.4 ± 9.10	87.2 ± 9.74
Mean BMI (kg m^{-2})	34.8 ± 7.84	35.5 ± 8.20

BMI, body mass index; BP, blood pressure; HCTZ, hydrochlorothiazide.

Table 2 | Median baseline laboratory values for the intent-to-treat population

	B+A (*n*=153)	B+HCTZ (*n*=151)	*P*-value
U alb:Cr ratio (mg g^{-1})			
Median	56.9	64.2	0.24
Range	10.3–570	15.9–693	
n	148	146	
Estimated GFR (ml min^{-1})			
Median	91.6	89.6	0.80
Range	47.1–180	45.2–175	
n	153	150	
Insulin resistance (HOMA-IR)			
Median	5.20	5.60	0.68
Range	0.50–43.0	0.50–104	
n	146	140	
Albuminuria (g per 100 ml)			
Median	4.20	4.20	0.65
Range	2.50–5.60	3.00–4.80	
n	153	150	
BNP (pg ml^{-1})			
Median	17.0	22.0	0.04
Range	4.99–336	4.99–383	
n	148	142	
hs-CRP (mg per 100 ml)			
Median	0.32	0.32	0.49
Range	0.00–5.28	0.02–15.8	
n	148	148	

BNP, B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate; HCTZ, hydrochlorothiazide; HOMA-IR, homeostasis model assessment of insulin resistance; Ualb:Cr, urinary albumin-to-creatinine.

prematurely discontinued from the study primarily due to adverse events (AEs), being lost to follow-up, unsatisfactory therapeutic effect, or withdrawal of consent (Figure 1). Among the patients who discontinued, 13 patients in the B + A arm and 15 patients in the B + HCTZ arm had one post-baseline assessment conducted and were included in the intent-to-treat population. Thus, the intent-to-treat population included 153 patients in the amlodipine/benazepril and 151 patients in the B + HCTZ treatment groups. The safety population included all 332 randomized patients (166 per treatment group).

The demographic and clinical characteristics of the two treatment groups were similar (Table 1). The median baseline laboratory parameters for efficacy variables were not significantly different between treatment groups (Table 2), except for a lower B-type natriuretic peptide levels (BNP) in the B + A group (17.0 vs 22.0 pg ml^{-1}; $P = 0.0369$) (Table 2). All patients in both treatment groups underwent the placebo run-in phase and were administered a dose of B + A 20/5 mg or B + HCTZ 20/12.5 mg, respectively, at the time of

randomization. Approximately 85% in both treatment groups required titration to the next dose level (B + A 40/5 mg, $n = 147$; B + HCTZ 40/12.5 mg, $n = 141$), and approximately 70% of these participants in both treatment groups required titration to maximal doses (B + A 40/10 mg, $n = 124$; B + HCTZ 40/25 mg, $n = 114$). Concomitant antihypertensive rescue medication use was similar between the two treatment groups. The most frequent concomitant antihypertensive rescue medications used in both arms were selective β-blocking agents (27.7% in each group), and the most frequently used β-blocking agent was metoprolol succinate (18.7% in the B + A group and 16.3% in the B + HCTZ group). A slightly higher percentage of subjects in the B + A group than that in the B + HCTZ group used the following concomitant medications: biguanides (57.2 vs 42.8%, respectively); macrolides (13.3 vs 6.0%, respectively); and adrenergics and other drugs for obstructive airway disease (11.4% vs 3.0%, respectively).

Primary outcome

Both B + A and B + HCTZ significantly decreased the median percent change in the Ualb:Cr ratio from baseline to end of the study for the entire cohort. There was a smaller percent change from baseline in the B + A group (median percent change: −40.5%; range: −98.3 to 880%) than that in the B + HCTZ group (median percent change: −72.1%; range: −98.4 to 590%) ($P < 0.0001$) (Figure 2). Using the ANCOVA (analysis of covariance) model and after adjusting for baseline BNP and reduction in BP as covariates, similar results were observed, with smaller reductions in the Ualb:Cr ratio from baseline in the B + A group (median change: $-17.4\,mg\,g^{-1}$; range: -281 to $365\,mg\,g^{-1}$) than that in the B + HCTZ group (median change: $-43.0mg\,g^{-1}$; range: -611 to $378\,mg\,g^{-1}$) ($P = 0.0003$).

Reductions from baseline in sitting SBP and DBP were significant in both treatment groups ($P < 0.0001$) (Figure 3). The mean reduction in both SBP and DBP was greater in the B + A arm than in the B + HCTZ arm; however, significance in favor of B + A was observed only for DBP (SBP: −20.5 vs −18.8, $P = 0.19$; DBP: −13.1 vs −9.97, $P = 0.02$; Figure 3).

A greater proportion of patients who had microalbuminuria at baseline and treated with B + HCTZ compared with B + A attained normalization of the Ualb:Cr ratio, defined as $< 30\,mg\,g^{-1}$ (69.2 vs 47.8%; $P = 0.0004$) (Figure 4).

Subgroup analyses

Subgroup analyses revealed small but significant differences between groups in both the absolute and percent change from baseline in the Ualb:Cr ratio for age ($P < 0.0001$), high and low stratum ($P = 0.0012$ and $P < 0.001$, respectively), and SBP ($P < 0.05$). There were no differences between treatment

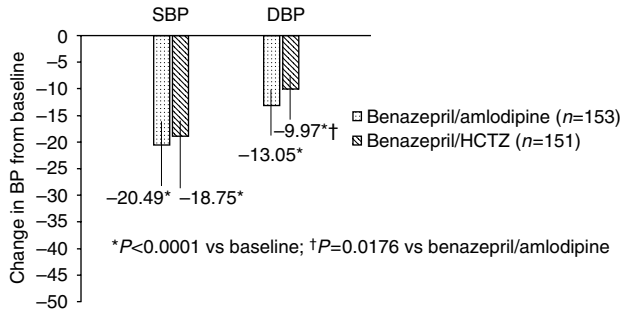

Figure 3 | Mean change in sitting systolic and diastolic blood pressure from baseline at Week 52 by treatment group. SBP, systolic blood pressure; DBP, diastolic blood pressure.

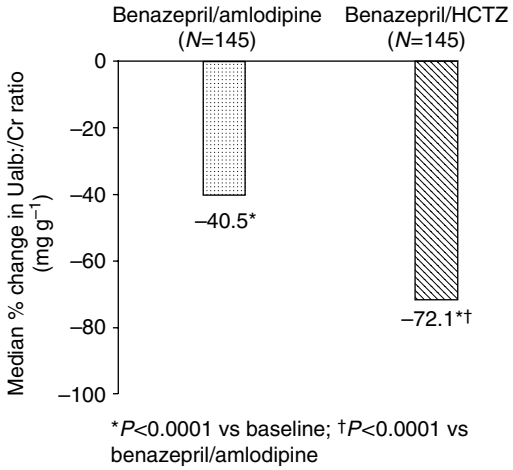

Figure 2 | Median percent change in the urinary albumin-to-creatinine (Ualb:Cr) ratio from baseline at week 52 (LOCF) for the entire intent-to-treat cohort. Note: Baseline data was available for 148 patients in the benazepril/amlodipine group and 146 patients in the benazepril/HCTZ group. At the end of the study (week 52, last observation carried forward; LOCF) data were available for only 145 patients in each group. HCTZ, hydrochlorothiazide.

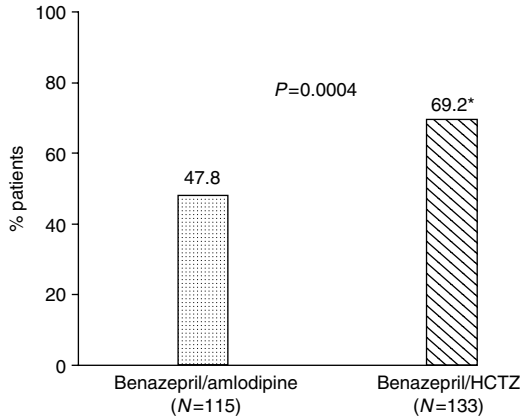

Figure 4 | Proportion of patients with microalbuminuria only who attained normalization of the urinary albumin-to-creatinine (Ualb:Cr) ratio ($< 30\,mg\,g^{-1}$) by the end of the study (intent-to-treat population). Baseline data were available for 148 patients in the benazepril/amlodpine group and 146 patients in the benazepril/HCTZ group. The data shown exclude patients who had a baseline Ualb:Cr ratio of $< 30\,mg\,g^{-1}$ (benazepril/amlodipine: 33 patients and benazepril/HCTZ 13 patients).

groups in the primary efficacy variable in patients ⩾65 years ($P=0.3828$) or in patients with a SBP between 120 and 129 mm Hg at end of the study ($P=0.0715$). In all SBP subgroups, the median percent decrease from baseline in the Ualb:Cr ratio was significantly smaller in the B + A treatment group than that in the B + HCTZ group ($P<0.05$).

We also conducted an exploratory analysis in patients with baseline Ualb:Cr ratio between 30 and 300 mg g^{-1} for primary efficacy variable. In this analysis, differences between the two treatment groups for median percent change from baseline in the Ualb:Cr ratio were similar to those observed in the entire study population with smaller percent change in the B + A group (−46.3%, range: −98.3 to 265) than that in the B + HCTZ group (−73.0%, range: −98.4 to 590%), $P<0.001$). As observed with the entire study population, a greater proportion of patients treated with B + HCTZ than with B + A attained normalization of the Ualb:Cr ratio, defined as <30 mg g^{-1} (76.5 vs 52.4%; $P=0.0001$).

Rates of progression to overt diabetic nephropathy, that is, >300 mg g^{-1} creatinine, by end of the study were similar between the two groups (4.6 vs 4.0%; $P=0.7901$). In a logistic regression analysis, there were no associations of treatment, age, race, baseline SBP, baseline DBP, baseline HbA_{1c} (hemoglobin A_{1c}), and baseline albuminuria with the development of overt diabetic nephropathy by week 52 ($P>0.05$ for all variables).

Secondary outcome

No significant differences were found for other secondary laboratory efficacy measures at end of the study, including changes in HOMA-IR (homeostasis model assessment of insulin resistance) ($P=0.30$), albuminuria ($P=0.83$), BNP ($P=0.83$), or high-sensitivity C-reactive protein (hs-CRP; $P=0.33$). In contrast, the mean decrease in the estimated glomerular filtration rate (eGFR) over the 52-week period was less in the B + A group than in the B + HCTZ group (−2.03 ± 14.2 vs −13.64 ± 16.1 ml min^{-1}; $P<0.0001$) (Figure 5). Additionally, we tested for an interaction between baseline BNP differences and change in albumin:creatinine; however, a significant interaction was not present ($P=0.99$).

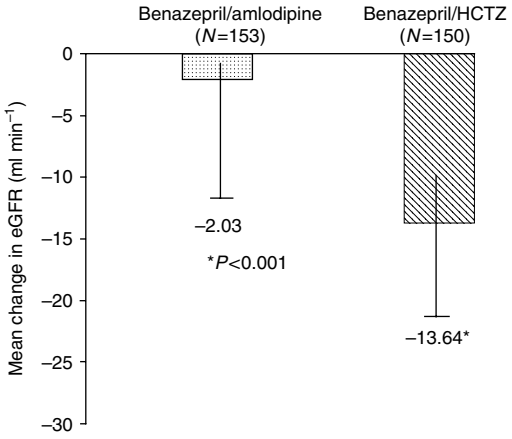

Figure 5 | Mean change in estimated glomerular filtration rate (eGFR) from baseline to end of study. Baseline data were available for 153 patients in the benazepril/amlodipine group and 150 patients in the benazepril/HCTZ group. End of the study (week 52, LOCF) data were available for all patients with a baseline measurement.

Table 3 | Summary of AEs occurring in ⩾5% of patients in either treatment group (safety population)

AE	Number (%) of patients	
	Benazepril/amlodipine (*n*=166)	Benazepril/HCTZ (*n*=166)
Peripheral edema	29 (17.5)	12 (7.2)
Cough	23 (13.9)	17 (10.2)
Upper respiratory tract infection	16 (9.6)	16 (9.6)
Dizziness	15 (9.0)	11 (6.6)
Headache	14 (8.4)	16 (9.6)
Bronchitis	14 (8.4)	12 (7.2)
Diarrhea	14 (8.4)	11 (6.6)
Arthralgia	14 (8.4)	13 (7.8)
Fatigue	13 (7.8)	13 (7.8)
Back pain	13 (7.8)	10 (6.0)
Muscle spasms	11 (6.6)	7 (4.2)
Nasopharyngitis	10 (6.0)	13 (7.8)
Urinary tract infection	10 (6.0)	8 (4.8)
Nausea	7 (4.2)	11 (6.6)
Pain in extremity	7 (4.2)	11 (6.6)

AE, adverse event; HCTZ, hydrochlorothiazide.

Side effects

Overall, both study drugs were well tolerated. AEs occurring in ⩾5% of patients in either treatment group regardless of relationship to study drug are summarized in Table 3. The most frequently reported AEs of suspected relationship to study drug occurred in the general disorders and administration site conditions system organ class (11.4 and 3.6% in the B + A and B + HCTZ groups, respectively) and included peripheral edema (7.8 vs 2.4%, respectively), fatigue (1.2% in each group), pitting edema (1.2 vs 0%, respectively), face edema (0.6 vs 0.0%, respectively), and thirst (0.6 vs 0.0%, respectively). More patients in the B + HCTZ group (18; 10.8%) than in the B + A group (9; 5.4%) discontinued study drug treatment due to AEs. The most common reasons for discontinuation were cardiac disorders (2; 1.8%), peripheral edema (1; 0.6%), infections (2;1.2%), benign neoplasms (1; 0.6%), thoracic events (2; 1.2%), and hypotension (1; 0.6%) in the B + A group and cardiac disorders (3; 1.8%), peripheral edema (1; 0.6%), fatigue (1; 0.6%), asthenia (1; 0.6%), metabolic disorders (2; 1.2%), nervous system disorders (4; 2.4%), vascular disorders (2; 1.2%), and thoracic disorders (4; 2.4%) in the B + HCTZ group. The three deaths that occurred (one in the B + A group and two in the B + HCTZ group) were not considered to be related to study drug treatment.

DISCUSSION

Clinical practice guidelines uniformly recommend that initial treatment of hypertension in those with diabetes or kidney disease include either an ACE inhibitor or an angiotensin

receptor blocker (ARB).[1,4,8] However, such guidelines do not provide consistent recommendations for a second drug class if needed to achieve BP goal of $<130/80$ mm Hg. Large-scale, randomized, multicenter trials of both ACE inhibitors and ARBs in patients with kidney disease (similar to our cohort) have demonstrated reduction in microalbuminuria.[10,11] However, in these trials, the ACE inhibitor and ARBs were used as monotherapy. Both CCB and diuretics when added to either an ACE or an ARB further reduce BP; however, the impact on albuminuria was previously unknown. In the Reduction of End points in NIDDM (non-insulin-dependent diabetes mellitus) With the Angiotensin II Antagonist Losartan (RENAAL) Study,[12] the use of amlodipine as a concurrent therapy to losartan yielded a similar outcome as seen for the losartan cohort with no difference in albuminuria reduction compared with the participants who did not use amlodipine. The principal new finding in our study was that in hypertensive patients with diabetes and microalbuminuria, both fixed-dose combinations of the ACE inhibitor benazepril, with CCB, amlodipine, or with the diuretic hydrochlorothiazide reduce the Ualb:Cr ratio. We also found that the reduction in the Ualb:Cr ratio was significantly greater with B + HCTZ combination than with B + A combination, both in the entire population and in patients with baseline Ualb:Cr ratio between 30 and 300 mg g^{-1}. However, the mean rate of decline in GFR was slower in those randomized to the B + A than those randomized to the B + HCTZ combination that may have affected the changes in microalbuminuria. Thus, our study findings did not support our hypothesis of no difference in albuminuria given similar levels of BP reduction with either ACE/CCB or ACE/diuretic combination.

The reasons for the greater reduction in Ualb:Cr in the B + HCTZ group cannot be determined from our study. Possible explanations include greater reductions in eGFR in the diuretic group as well as differences in preexisting volume status. Although there were no interactions between BNP and albuminuria in our study, it should be noted that the plasma levels of BNP are increased in people consuming a high level of sodium.[13] High sodium intake generally blunts the antiproteinuric effects of RAS blockers; however, the use of thiazide diuretics overcomes this blunting effect.[14–16] Unfortunately, in our study, we could not definitely ascertain whether the difference in volume reflected by baseline BNP contributed to the differences in albuminuria, as we did not monitor urinary sodium levels. Thus, the greater decrease in Ualb:Cr in the B + HCTZ group should be interpreted with caution.

There is limited information available on the influence of diuretics on urinary albumin excretion.[17,18] Whereas some investigators have reported no effect of thiazide diuretics on albumin excretion,[19] others have reported an increase in microalbuminuria with diuretics.[20] However, studies have reported that the addition of hydrochlorothiazide can overcome the blunting of the therapeutic efficacy of ACE inhibition on proteinuria caused by high sodium intake.[14] Indeed, increased dietary salt intake is well known to offset the antiproteinuric effects of not only blockers of the renin–angiotensin system but also that of CCBs.[21] The protocol used in our study did not mandate restriction on salt intake. Future trials of fixed-dose combinations with similar base components should consider protocol-driven control of sodium intake and the measurement of urinary sodium and blood BNP at baseline to isolate and handle this potential source of confounding.

Another factor that may account for differences in albuminuria is the relatively greater reduction in eGFR over the study duration. Estimated GFR was calculated using the modified MDRD (Modification of Diet in Renal Disease Study Group) equation reported by Levey *et al.*[22] and the modification for Blacks when appropriate.[23] The difference in eGFR between the groups may have reflected additional volume depletion, although side effect profiles were not different between groups. Given that, the cohort had stage 1 and early stage 2 nephropathy at baseline, a change in the eGFR seen in the B + HCTZ group may have contributed to the further reduction in albuminuria through decreased filtration.

In this study, there was no difference in change from baseline in sitting SBP between the two treatment groups; however, there was a significantly larger mean decrease from baseline in sitting DBP in the B + A arm (Figure 2). This difference in BP would normally be expected to yield a greater antialbuminuric effect, but did not in this case. In this study, 81 patients (53%) in the B + A arm and 78 patients (52%) in the benazepril/hydrochorothiazide arm had a SBP <130 mm Hg at end of the study. Although the number of patients achieving target goal of DBP <80 mm Hg and combined BP goal of $<130/80$ mm Hg was not measured, the greater reduction in the DBP achieved with the B + A arm reflects better BP control.

Both B + A and B + HCTZ treatment were well tolerated in our study. AEs generally were of mild or moderate severity and were similar to those previously reported for ACE inhibitors, CCB, and diuretics.

Albuminuria is recognized as an important predictor of the risk of progression to ESRD and the risk of cardiovascular events. However, this study does not allow us to extrapolate the results obtained to make conclusions around the potential impact on cardiovascular risk for the medications studied. Notably, the ongoing ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension) study, a 12 000 patient mortality trial testing the same drug combinations in GUARD, will shed further light on this issue in the context of cardiovascular outcomes and kidney disease progression, as the albumin:creatinine ratio and change in eGFR are being assessed as pre-specified secondary end points.

In conclusion, both initial fixed-dose combinations of benazepril/diuretic and B + A in hypertensive patients with type II diabetic nephropathy resulted in significant reductions in BP and urinary albuminuria with high rates of normalization of the albumin:creatinine ratio and low ($<5\%$) rates of progression to overt proteinuria over 1 year.

MATERIALS AND METHODS

Study design and patient population

GUARD was a 1-year, multicenter, randomized, double-blind parallel-group study designed by the primary investigator in conjunction with the sponsor, Novartis Pharmaceuticals Corporation, that assessed the efficacy and tolerability of combination antihypertensive treatment with either B + A or B + HCTZ to decrease the Ualb:Cr ratio. Eligible subjects were men or women aged 21–85 years with type II diabetes mellitus, albuminuria (defined as a Ualb:Cr ratio between 20 and 500 mg g^{-1} confirmed in at least two of three consecutive morning urine specimens), and hypertension (mean SBP, $\geqslant$130 mm Hg and $<$180 mm Hg; mean DBP, $\geqslant$80 mm Hg and $<$110 mm Hg). Excluded from the study were persons with kidney disease not caused by diabetes and/or hypertension; confirmed or suspected renal artery stenosis; a cardiovascular disease event (myocardial infarction, stroke, transient ischemic attack, cardiovascular revascularization/angioplasty) within the previous 6 months; evidence of heart failure or documented left ventricular ejection fraction $<$40%; type I diabetes or uncontrolled type II diabetes (HbA_{1c} $>$9.5%); and a serum creatinine $>$1.5 mg per 100 ml for men and $>$1.3 mg per 100 ml for women. All patients gave written informed consent before entry into the study.

Eligible participants who entered the study had their ACE inhibitor, ARB, and aldosterone receptor blocker therapy withdrawn after screening phase. This was followed by a 3-week placebo run-in phase where all other antihypertensive agents were discontinued. At the end of the placebo run-in phase, participants were randomized to either B + A 20/5 mg or B + HCTZ 20/12.5 mg for 4 weeks to achieve the target BP of $<$130/80 mm Hg. Those who had not achieved the target BP were titrated at week 4 to B + A 40/5 mg or B + HCTZ 40/12.5 mg for additional 4 weeks. Doses were again titrated at week 8 to B + A 40/10 mg or B + HCTZ 40/25 mg in patients who had not achieved the target BP ($<$130/80 mm Hg). At week 12 and all subsequent visits, patients not meeting target BP were titrated to the next dose level and all patients titrated to B + A 40/10 mg or B + HCTZ 40/25 mg received add-on antihypertensives, including α-blockers, β-blockers, centrally acting antihypertensive agents, and direct vasodilators, to achieve target BP. Prohibited as add-on medications were other ACE inhibitors, ARBs, and aldosterone receptor blockers.

Outcomes

The primary outcome was change in the Ualb:Cr ratio from baseline to week 52. Secondary efficacy variables included the proportion of patients who progressed to overt diabetic nephropathy (as determined by a Ualb:Cr ratio of $\geqslant$300 mg g^{-1} by week 52), the change from baseline to week 52 in eGFR using the modified MDRD equation, the magnitude of albuminuria, the biomarkers BNP and hs-CRP, and insulin sensitivity (HOMA-IR). The safety and tolerability of combination treatment with B + A or B + HCTZ were assessed by monitoring and recording all AEs as well as monitoring clinical laboratory test results and findings from physical assessments. All laboratory tests were performed at a centralized lab.

Statistical methods

All statistical tests in this noninferiority trial were conducted against a two-sided alternative hypothesis using a significance level of 0.05.[9] For testing the hypothesis of noninferiority of the CCB/ACE inhibitor treatment regimen and the ACE inhibitor/diuretic treatment regimen, a one-sided test was performed at the 2.5% level of significance (or equivalently, a 97.5% one-sided confidence interval for the difference will be used).[9] Tests for the superiority of the CCB/ACE inhibitor treatment regimen compared with the ACE inhibitor/diuretic treatment regimen were based on the null hypothesis, and a two-sided test will be performed at the 5% significance level.[9]

The sample size was determined based on 90% power, assuming no difference in the change from baseline to week 52 in the Ualb:Cr ratio between B + A and B + HCTZ treatment regimens. The power calculations allowed for a dropout rate of 20% after randomization. Thus, a sample size of 334 randomized subjects (167 per group) was necessary for this study. To assess differences between the two groups for the primary efficacy variable, we assumed a difference of 44 mg g^{-1} in change in Ualb:Cr from baseline between groups with a s.d. of 106 mg g^{-1}. This yielded a two-sided significance level of 0.05, and an estimated number of evaluable patients of 304 (152 per group). In retrospect, using the final results in our assumptions, we find the power of the test is 95% (overpowered). Given the final results, only 246 (123 per group) evaluable patients were required to detect 90% power as planned.

Baseline demographic and clinical characteristics were summarized by treatment group with appropriate descriptive statistics. χ-Test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables were used to test for homogeneity between the treatment groups at baseline.

Efficacy analyses were performed using the intent-to-treat population, which included all randomized patients who received at least one dose of study medication during the active treatment phase and for whom there was at least one post-baseline efficacy measurement. The Wilcoxon rank-sum test was used for analyses of the primary efficacy variable, change from baseline in the Ualb:Cr ratio, as the data were not normally distributed. Because of the wide variability in the Ualb:Cr ratio, the percent change from baseline in the Ualb:Cr ratio was identified as being more clinically relevant statistic for analysis. In addition, the data were not normally distributed and had a wide deviation from the 'mean.' Hence, the 'median' was used to represent the change from baseline and the difference from baseline was tested using non-parametric analysis. The proportion of patients who progressed to overt nephropathy was analyzed using the Cochran–Mantel–Haenszel χ-test, adjusting by Ualb:Cr ratio strata (high: 211–500 mg g^{-1}; medium: 121–210 mg g^{-1}; low: 20–120 mg g^{-1}). Additionally, we also used ANCOVA to analyze the treatment effect on the Ualb:Cr ratio after adjusting for covariates of BP reduction and BNP.

Safety analyses were performed using the safety population, which included all randomized patients who received at least one dose of study medication during the active treatment phase. The incidence of AEs was summarized by primary organ system, preferred term, severity, and relationship to study drugs. The incidence of death, other serious AEs, and AEs leading to study discontinuation were summarized separately.

CONFLICT OF INTEREST

GLB, PAM and RDT have served as consultants and speakers for Novartis Pharmaceuticals Corporation. RR, DP and PD are employees at Novartis Pharmaceuticals Corporation.

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